## REMARKS

### I. SUBMISSION OF AMENDED (CORRECTED) FORMAL DRAWINGS

In the Preliminary Amendment filed August 20, 2002 (page 2), Applicants noted that several typographical errors were inadvertently made in the formal drawings for Figures 8A, 8B, 9G, and 9H that were filed in the instant application on November 26, 2001. Applicants explained that these errors were **not** present in the informal drawings for Figures 8A, 8B, 9G, and 9H originally filed with the application on June 22. 2001. Along with the Preliminary Amendment filed November 26, 2001, Applicants submitted annotated sheets for the formal drawing sheets 23/39 and 25/39, which expressly showed the changes proposed to be made to the formal drawings for Figures 8A, 8B, 9G, 9H to correct these errors. In that Preliminary Amendment, Applicants explained that these typographical errors were inadvertently introduced when the formal drawings were prepared and that the corrections were consistent with the informal drawings originally filed with the application. Applicants also explained that no new matter was introduced by these amendments. Applicants stated that the Examiner approved of these corrections, Applicants would re-submit corrected formal drawings.

Applicants hereby submit replacement sheets for formal drawing sheets 23/39 and 25/39 and annotated sheets showing the proposed amendments to Figures 8A, 8B, 9G, and 9H. These replacement sheets and annotated sheets are included in the Appendix attached hereto. These changes are explained in detail in the section entitled "Amendments to the Drawings" above. As explained therein, no new matter is introduced by these amendments. Entry of these amendments to the drawings is respectfully requested.

### II. STATUS OF THE CLAIMS

Claims 1-258 were cancelled previously. Claims 302-367 and 369-381 were previously withdrawn. Claims 259-301 and 368 were considered by the Examiner in the Office Action mailed September 24, 2004. Claims 264, 302-367, and 369-381 are canceled with the entry of this Amendment without restriction to subsequent revival, including in a divisional or continuation. Claims 259, 261, 262, 265, 269, 273, 275, 277, 278, 281, 283, 284, 285, 287, 290, 291, 292, 293, 297, and 298 have been amended. The amendments to these claims are fully supported by the specification as filed and no new matter has been added by these amendments. Claims 259, 261, 262,265, 269, 273, 275, 277, 278,281, 283, 284, 287, 292, 293, and 297 are

amended herein to delete the word "about". This amendment is not made in response to any rejection by the Examiner, but is simply made to specify more particularly a particular claim limitation.

Claim 285 has been amended to specify that the extracellular domain of the isolated or recombinant polypeptide of claim 284 comprises an amino acid sequence having at least 95% sequence identity to the subsequence of SEQ ID NO:66 that comprises at least amino acid residues 35-244. Support for this amendment is found throughout the specification, including at, e.g., claims 264, 265, 283 and page 87, lines 3-31.

Claim 298 has been amended to specify more particularly a pharmaceutical composition comprising the polypeptide of claim 259 and a pharmaceutically acceptable excipient. Support for this amendment is found throughout the specification, including at, e.g., page 50, lines 3-7. Additional amendments to the claims are discussed in detail below.

New claims 382-391 have been added. All of the claims are fully supported by the application as filed and no new matter has been added. For example, support for new claims 382-383 is provided in the specification, including at, but not limited to, e.g., page 87, lines 3-31; page 21, line 27 to page 22, line 5; page 62, lines 15-23; page 121, line 12 to page 123, line 18; page 188, lines 12-14; page 189, lines 23-26; and page 204, lines 1-7.

Support for new claim 384 is provided in the specification, including at, but not limited to, e.g., original claim 4, page 87, lines 3-31; page 121, line 12 to page 123, line 18; page 21, lines 27-31; page 62, lines 15-19; page 121, line 12 to page 123, line 18; page 188, lines 12-14; and page 189, lines 23-26.

Support for new claim 385 is provided in the specification, including at, but not limited to, e.g., original claims 4-5; page 87, lines 3-31; page 21, line 27 to page 22, line 5; page 62, lines 15-23; page 121, line 12 to page 123, line 18; page 188, lines 12-14; and page 189, lines 23-26.

Support for new claim 386 is provided in the specification, including at, but not limited to, e.g., original claims 4-5; page 87, lines 3-31; page 21, line 27 to page 22, line 5; page 62, lines 15-23; page 121, line 12 to page 123, line 18; page 188, lines 12-14; and page 189, lines 23-26.

Support for new claim 387 is provided in the specification, including at, but not limited to, e.g., original claims 4-5; page 87, lines 3-31; page 21, line 27 to page 22, line 5; page 62, lines 15-23; page 121, line 12 to page 123, line 18; page 188, lines 12-14; and page 189, lines 23-26.

Support for new claim 388 is provided in the specification, including at, but not limited to, e.g., original claims 4-5; page 87, lines 3-31; page 21, line 27 to page 22, line 5; page 62, lines 15-23; page 121, line 12 to page 123, line 18; page 188, lines 12-14; and page 189, lines 23-26.

Support for new claims 389-391 is provided throughout the specification, including at, e.g., original claim 41 and page 50, lines 3-7.

## III. OBJECTIONS TO THE SPECIFICATION AND CLAIMS

In paragraph 1 of the Office Action (page 2), the Examiner states that the sequence disclosed in claim 291 is not accompanied by SEQ ID numbers. Claim 291 has been amended to include the sequence identification number (SEQ ID NO:284) for the sequence disclosed in the claim. Support for this amendment is provided in the specification, including, but not limited to, e.g., page 111, line 11. This sequence was provided in the Sequence Listing submitted previously and Applicants are in compliance with the requirements of 37 CFR §§ 1.821-1.825.

In paragraph 4 of the Office Action (page 3), the Examiner states that a new title is required that is indicative of the invent to which the elected claims are directed. The title has been amended herein to recite "Co-Stimulatory Polypeptides".

In paragraph 6 of the Office Action (page 3), the Examiner states that the proper trademark should be used for FastTrack® 2.0 mRNA Isolation Kit on page 178, line 26 of the specification. The specification has been amended to recite the proper trademark for the FastTrack® 2.0 mRNA Isolation Kit, as specified by Invitrogen. The entire trademark need not be capitalized. In this instance, the trademark is distinguished by capitalization of the first letter of the trademark and by using the symbol ® to identify the term as a registered trademark. The generic terminology follows the registered trademark symbol.

The specification has been similarly amended on page 178, line 27 to recite the proper trademark for the Promega RNAgents® Total RNA Isolation System Kit, as specified by Promega, and on page 179, lines 5-6 to recite the proper trademark for the Invitrogen cDNA Cycle® Kit, as specified by Invitrogen. In each instance, the trademark is distinguished by capitalization of the first letter of the trademark and by using the symbol ® to identify the term as a registered trademark. Generic terminology follows the registered trademark symbol.

The specification has also been amended in the paragraph beginning on page 52, line 26 to eliminate browser-executable code, as requested by the Examiner in paragraph 6 of the Office Action (page 4).

In paragraph 7 of the Office Action (page 4), the Examiner objects to claim 264 as being a duplicate of claim 263. Applicants note that two different claims, each numbered as claim 264, were inadvertently included. To alleviate any confusion and to overcome the objection, claim 264 that is identical to claim 263 has been canceled. The remaining claim 264, which specifies the isolated or recombinant polypeptide of claim 259, wherein the polypeptide further comprises a signal peptide, is proper and has not been canceled. Withdrawal of the objection is respectfully requested.

## IV. AMENDMENTS TO THE SPECIFICATION

The specification has also been amended to correct a number of inadvertent typographical errors. For example, the specification has been amended at page 23, line 8 to state correctly that Figure 8B shows schematic representations of the amino acid sequences of CD28BP-15 (not CD28BP-12), as was clearly shown in Figure 8B originally filed with the application.

In addition, the specification has been amended to correct several inadvertent typographical errors in the terms "CD28/CTLA-4 binding affinity ratio" and "CTLA-4/CD28 binding affinity ratio". Support for these amendments is provided through the specification, including at, but not limited to, e.g., page 43, lines 10-20. The binding affinity ratio refers to the receptors -- CD28 and CTLA-4 -- for B7-1 and the novel polypeptides of the invention. The binding affinity ratio does not include the term "CD28BP" (which represents a CD28 binding protein, not the CD28 receptor) and does not include the term CTLA-4BP (which represents the CTLA-4 binding protein, not the CTLA-4 receptor).

The specification has also been amended in the paragraph beginning on page 59, line 27 and the paragraph beginning at page 222, line 20 to include the serial number for a commonly assigned U.S. Patent Application entitled "Novel Chimeric Promoters" filed June 21, 2001.

Furthermore, as discussed in greater detail below, the specification has been amended to correct several inadvertent errors in the trademark terms and to remove eliminate browser-executable code.

## V. REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 259-296, 298, 301, and 368 were rejected under 35 USC § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention, as set forth below. Office Action, pages 4-5.

(A) The Examiner finds that claims 259 and 291 and claims dependent thereon are ambiguous in that it is unclear whether the phrase "expressed on a cell or bound to a cell membrane" is intended to refer to "human B7-1" or "the isolated or recombinant polypeptide." The claims have been amended to specify more clearly "when the isolated or recombinant polypeptide is expressed on a cell or bound to a cell membrane." Support for this amendment is provided in the specification, including, but not limited to, e.g., page 21, line 27 to page 22, line 5; page 62, lines 15-23; page 188, lines 12-14; and page 189, lines 23-26. Withdrawal of the rejection is respectfully requested.

(B) The Examiner finds that there is insufficient antecedent basis in claim 290 for the limitation "the polypeptide of claim 288, wherein the modified amino acid...." Claim 290 has been amended to correct the claim dependency. Applicants thank the Examiner for his careful review of the claims. Withdrawal of the rejection is respectfully requested.

(C) The Examiner finds that claim 291 and claims dependent thereon are ambiguous in the recitation of the phrase "residues at positions 35 – 244", and it is unclear to which sequence these numbers refer. The rejection has been overcome by amending claim 291 to include the sequence identification number (SEQ ID NO:284) to which the residue positions refer. Support for this amendment is provided in the specification, including, but not limited to, e.g., page 111, line 11. Withdrawal of the rejection is respectfully requested.

## VI. REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH

### A. The Claims Are Sufficiently Described

Claims 261-264, 269-270, 273, 276-277, 284-285, 292, 296, and 299-301 were rejected under 35 USC § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Office Action, page 5. The Examiner states that this is a new matter rejection. Specifically, the Examiner is of the view that "the following ranges of amino acid residues of SEQ ID NO:66,

claimed in the claims listed above, represent a departure from the specification and the claims as originally filed, and applicant has not pointed out where the support comes from: '35-244, 35-245, 245-268, 246-272, 269-303, 273-303, 35-303, 1-268, and 1-272.'" This rejection is respectfully traversed as follows.

Compliance with the written description requirement of § 112 requires that sufficient information be included in the original disclosure to show that the inventor(s) possessed the invention at the time of the original filing. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1320, 66 USPQ2d 1429, 1438-39 (Fed. Cir. 2003), *rehearing denied* (Apr. 25, 2003); p*etition for cert. filed*, 72 U.S.L.W. 3106 (U.S. Jul. 24, 2003) (No. 03-124). *Moba* stressed that "[t]he written description requirement does not require the applicant to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. . . .'" *Moba*, 352 F.3d at 1320-1321, 66 USPQ2d at 1439, quoting *Union Oil Co. of Cal. V. Atlantic Richfield Co.*, 208 F.3d 989,997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000).

Support for the recited ranges of amino acid residues of SEQ ID NO:66 in these claims – specifically, 35-244, 35-245, 245-268, 246-272, 269-303, 273-303, 35-303, 1-268, and 1-272 – is clearly provided in the specification as filed. In the Preliminary Amendment filed on August 20, 2002, Applicants provided explicit detail of the support in the specification for each of the claims, including claims 261-264, 269-270, 273, 276-277, 284-285, 292, 296, and 299-301, which are the subject of this rejection. See, e.g., pages 16-23 of the Preliminary Amendment filed on August 20, 2002.

For the convenience of the Examiner, Applicants again identify the support in the specification for these recited amino acid residue ranges below.

The specification explains that the amino acid sequence of wild-type full-length human B7-1 (SEQ ID NO:278) comprises 288 amino acids, of which the signal peptide comprises amino acid residues 1-34, the extracellular domain (ECD) comprises amino acid residues 35-242, the transmembrane domain comprises amino acid residues 243-263, and the cytoplasmic domain comprises amino acid residues 264-288. The specification also explains that the mature form of human B7-1 (i.e., the full-length sequence without the signal peptide) has a total of 254 amino acids and comprises amino acid residues 35-288. See, e.g., page 26, line 27 to page 27, line 3.

The specification notes that the polypeptide sequence of wild-type (naturally-occurring) human B7-1 is shown in SEQ ID NO:278. The specification further explains that Figures 2A-2H depict an alignment of the human B7-1 polypeptide sequence (SEQ ID NO:278) with a number of exemplary CD28BP polypeptide sequences of the invention, including SEQ ID NO:66. Figures 2A-2H show predicted boundaries between the signal peptide region, extracellular domain, transmembrane domain, and cytoplasmic domain for these CD28BP polypeptide sequences, based on comparison with the predicted boundaries for those regions/domains in the human B7-1 sequence (SEQ ID NO:278). See, e.g., page 22, lines 6-13. The specification explains that the signal peptide, extracellular domain, transmembrane domain, and cytoplasmic domain of a polypeptide of the invention can be determined, for example, ***by comparison by amino acid alignment with a corresponding domain of human B7-1 sequence*** (SEQ ID NO:278). See, e.g., page 122, lines 7-27. The specification indicates that a predicted signal peptide of a novel costimulatory molecule (NCSM) polypeptide of the invention sequence can comprise the first 34 amino acids of the polypeptide. See, e.g., page 209, lines 11-12. Thus, for example, the signal peptide of human B7-1 (SEQ ID NO:278) comprises amino acid residues 1-34 and by comparison by alignment, a predicted signal peptide of SEQ ID NO:66 (clone CD28BP-15) comprises amino acid residues 1-34.

The extracellular domain of human B7-1 (SEQ ID NO:278) comprises amino acid residues 35-242, as indicated in the specification at, e.g., page 26, lines 29-30. Amino acid residue 242 of SEQ ID NO:278, which is N (asparagine), corresponds to amino acid residue 244 in SEQ ID NO:66, as shown in Fig. 2G. Thus, as explained in the specification, by comparison by alignment, a predicted extracellular domain of SEQ ID NO:66 comprises at least amino acid residues **35-244** of SEQ ID NO:66. The numbering of the extracellular domains for the human B7-1 (SEQ ID NO:278) and CD28BP-15 (SEQ ID NO:66) polypeptides differs because the predicted ECD of CD28BP-15 has two additional amino acid residues compared to that of human B7-1 (see, e.g., Figs. 2A-2H).

The specification also shows that in an alternative aspect the predicted signal sequence and extracellular domain of CD28BP-15 (SEQ ID NO:66) comprises amino acid residues 1-245. See the specification at, e.g., page 209, lines 6-13 and Table 5. Without the signal peptide, which comprises the first 34 amino acids of the polypeptide, this predicted extracellular domain of CD28BP-15 (SEQ ID NO:66) comprises at least amino acid residues **35-245**. *Id.*

In human B7-1 and the CD28BP polypeptides of the invention, the transmembrane domain follows the extracellular domain, as shown in Figure 2G. The transmembrane domain of

human B7-1 (SEQ ID NO:278) comprises amino acid residues 243-263, as indicated in the specification at, e.g., page 26, lines 30-31. By comparison by alignment, amino acid residue 243 of SEQ ID NO:278 corresponds to residue 245 of CD28BP-15 (SEQ ID NO:66), and amino acid residue 263 of SEQ ID NO:278 corresponds to amino acid residue 268 of CD28BP-15 (SEQ ID NO:66), as shown in Figure 2G. Thus, a predicted transmembrane domain of CD28BP-15 (SEQ ID NO:66) comprises at least amino acid residues **245-268**.

In human B7-1 and the CD28BP polypeptides of the invention, the cytoplasmic domain follows the transmembrane domain, as shown in Figure 2G. The cytoplasmic domain of human B7-1 (SEQ ID NO:278) comprises amino acid residues 264-288, as indicated in the specification at, e.g., page 26, line 31. By comparison by alignment, amino acid residue 264 of SEQ ID NO:278 corresponds to residue 269 of CD28BP-15 (SEQ ID NO:66), and residue 288 of SEQ ID NO:278 corresponds to residue 303 of CD28BP-15 (SEQ ID NO:66), as shown in Fig. 2G. Thus, a predicted cytoplasmic domain of SEQ ID NO:66 comprises at least amino acid residues **269-303**.

The specification also shows that in an alternative aspect the transmembrane domain of CD28BP-15 (SEQ ID NO:66) comprises at least amino acid residues 272-303. This is shown in the informal drawing for Figure 8B originally filed with the application and the amended formal drawing for Figure 8B submitted herewith (see replacement sheet 25/39). Originally filed Figure 8B and amended Figure 8B show by dashed line under the CD28BP-15 sequence (SEQ ID NO:66) that a predicted transmembrane domain begins with leucine (L) at amino acid residue position 246 of the CD28BP-15 protein sequence, ends with histidine (H) at position 272, and comprises the following residues: LPFWVIIPVSGALVLTAVVLYCLACRH. Thus, in this alternative aspect shown in Figure 8B, the predicted transmembrane domain of CD28BP-15 (SEQ ID NO:66) comprises at least amino acid residues **246-272**. In this instance, the predicted cytoplasmic domain of CD28BP-15 (SEQ ID NO:66), which follows the transmembrane domain as shown in Figure 8B and Figure 2G, comprises at least amino acid residues **273-303** (see Fig. 8B).

As explained in the specification, the mature domain of human B7-1 (SEQ ID NO:278), which constitutes the full-length protein sequence without the signal peptide, comprises amino acid residues 35-288. See, e.g., page 26, line 27 to page 27, line 2. Amino acid residue 288 of SEQ ID NO:278 corresponds to amino acid residue 303 of SEQ ID NO:66, as shown in Fig. 2G. Thus, by comparison by alignment (see, e.g., Figures 2A-2G), a predicted mature domain of CD28BP-15 (SEQ ID NO:66) comprises at least amino acid residues **35-303**.

A subsequence of human B7-1 (SEQ ID NO:278) corresponding to the signal peptide, extracellular domain, and transmembrane domain comprises amino acid residues 1-263 of SEQ ID NO:278. See the specification, e.g., at page 26, line 27-31 and Figures 2A-2H. As discussed above, in one format, a predicted transmembrane domain of CD28BP-15 ends with amino acid residue 268. Amino acid residue 268 of CD28BP-15 (SEQ ID NO:66) corresponds to amino acid residue 263 of SEQ ID NO:278, as shown in Fig. 2G. Thus, in this aspect, by alignment comparison, the predicted amino acid sequence corresponding to the signal peptide, extracellular domain, and transmembrane domain of SEQ ID NO:66 comprises at least amino acid residues **1-268** of SEQ ID NO:66.

In an alternative format, as discussed above and shown in the specification, a predicted transmembrane domain of CD28BP-15 comprises residues 246-272 of CD28BP-15 (SEQ ID NO:66). Based upon this format, an amino acid sequence corresponding to the signal peptide, extracellular domain, and transmembrane domain of SEQ ID NO:66 comprises at least amino acid residues **1-272** of SEQ ID NO:66.

Applicants respectfully submit that all of the rejected claims meet the written description requirement. As shown in detail above, each of the ranges of amino acid residues recited in the claims is described and fully supported in the specification as originally filed. One of ordinary skill in the pertinent art would certainly have recognized that the inventors had possession of the invention at the time of filing. Each claim clearly meets the written description requirement set forth in 35 USC § 112, first paragraph, and no new matter has been included in any of the pending claims. For at least these rejections, this rejection is wholly improper. Withdrawal of the rejection is respectfully requested.

The Examiner is of the view that the recitation of "binding affinity ratio about greater than" in claim 292 represents a departure from the specification and claims as originally filed. Office Action, page 6. This rejection is traversed in part and overcome in part. Applicants traverse this rejection because the specification specifies that the CD28/CTLA-4 binding affinity ratio is at least *about equal to or greater than* the CD28/CTLA-4 binding affinity ratio of human B7-1. See the specification, including at, but not limited to, e.g., page 43, lines 10-20. The word "about" modifies both "equal to" and "greater than." Thus, the specification clearly supports the phrase "binding affinity ratio about greater than." Although Applicants traverse this rejection and do not concede with the Examiner's position, in an effort to expedite, claim 292 has been amended to delete

the term "about." Claim 292, as amended, finds support in the specification, including at, but not limited to, e.g., original claim 21. With this amendment, this rejection of claim 292 is overcome.

**B. The Claims Are Sufficiently Enabled**

Claims 259-262, 265-278, 280-290, and 298 were rejected under 35 USC § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to enable one skilled in the art to which it is most nearly connected, to make and/or use the invention. Office Action, page 6. Specifically, the Examiner takes the position that "the limitations of 'extracellular domain,' 'signal peptide', transmembrane domain,' 'mature domain,' and cytoplasmic domain,' as they refer to the sequences having a certain percent identity to SEQ ID NO:66, were not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention." *Id.* at pages 6-7 (emphasis in original). The Examiner concedes that the definitions of these domains as they refer to SEQ ID NO:66 are set forth in the specification. However, the Examiner asserts that "there is insufficient guidance in the specification with regard to the boundaries of the respective function [sic] domains in homologous sequences. Without sufficient guidance, the specific sequences which would encompass the functional domains are unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue." *Id.* at page 7. This rejection is respectfully traversed.

As explained in detail above under the Section VI (A), the predicted boundaries for each of the predicted functional domains of CD28BP-15 (SEQ ID NO:66) (e.g., signal peptide, extracellular domain, transmembrane domain, cytoplasmic domain, mature domain) are clearly described in the application as originally filed. Furthermore, the specification clearly describes polypeptide sequences having a particular percent identity to one or more of these functional domains. See the specification, including at, but not limited to e.g., page 87, lines 3-31. Based upon the teachings of the specification, including the specifically defined nature of the claimed invention, the detailed guidance provided in the specification, the state of the art, and the level of skill in the art at the time the application was filed, one of ordinary skill in the art to which this application pertains would undoubtedly have been reasonably able to make and use the polypeptides defined by these claims. No undue experimentation would have been required to make and use the polypeptides defined by claims 259-262, 265-278, 280-290 and 298.

Moreover, even if some experimentation would have been necessary to make and use the claimed polypeptides, which Applicants do not believe, such experimentation would clearly not support an enablement rejection of claims 289 and 290. *In re Wands*, 858 F.2d 731 (Fed. Cir., 1988); *Atlas Powder Co. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir, 1984). It has long been established that enablement is not precluded even if some experimentation is required, provided that the amount of experimentation is not "unduly extensive." *Atlas Powder*, 750 F.2d at 1576. In this instance, no unduly extensive experimentation would be needed to make and use the claimed polypeptides.

Claims 289 and 290 were also rejected under 35 USC § 112, first paragraph as allegedly lacking enablement. Office Action, page 7. The Examiner notes that claims 289 and 290 are directed to a polypeptide comprising a modified amino acid and that the specification discloses on page 17 and in claim 290 a number of possible chemical modifications of amino acids. *Id.* However, the Examiner contends that the specification fails to teach what modifications of the disclosed sequences can be tolerated that will allow the protein to function as claimed. This rejection is respectfully traversed.

Claim 289 is dependent upon claim 259. As amended, claim 259 specifies an isolated or recombinant polypeptide comprising an extracellular domain, said extracellular domain comprising an amino acid sequence having at least 91% sequence identity to a subsequence of the polypeptide sequence set forth in SEQ ID NO:66, wherein the subsequence is the extracellular domain of SEQ ID NO:66, and wherein the isolated or recombinant polypeptide has a human CD28/human CTLA-4 binding affinity ratio about equal to or greater than the human CD28/human CTLA-4 binding affinity ratio of human B7-1 when the isolated or recombinant polypeptide is expressed on a cell or bound to a cell membrane.

Claim 259 thus plainly specifies that the polypeptide must have a CD28/CTLA-4 binding affinity ratio that is about equal to or greater than that of human B7-1. Applicants' specification clearly describes methods for testing for binding of the polypeptides to CD28 receptor and CTLA-4 receptor, how to determine for such polypeptide the ratio of the relative binding affinity for each of CD28 and CTLA-4, and how to compare the CD28/CTLA-4 binding affinity ratio for such polypeptide to that for human B7-1. See the specification, including at, but not limited to, e.g., page 43, lines 10-20; page 180, line 31 to page 182, line 26; page 187, line 10 to page 190, line 19; and page 190, line 21 to page 203, line 7. Based upon the teachings of the specification, including

the abundant guidance provided in the specification, the particularly defined nature of the invention, the numerous working examples, the state of the art, and the level of skill in the art at the time the application was filed, one of skill would have been reasonably able to make and use the polypeptides defined by claim 259.

The Examiner's contention that claims 289 and 290 are not similarly enabled is entirely misplaced. Claim 289, which depends from claim 259, further specifies that the polypeptide comprises at least one modified amino acid. Amended Claim 290, which depends from claim 289, further recites that the modified amino acid is a glycosylated amino acid, a PEGylated amino acid, a farnesylated amino acid, an acetylated amino acid, a biotinylated amino acid, an amino acid conjugated to a lipid moiety, or an amino acid conjugated to an organic derivatizing agent. The Examiner asserts that the specification fails to provide to teach what modifications of the disclosed sequenced can be tolerated that will allow the protein to function as claimed. Office Action, page 8. The Examiner asserts that "the recitation of a range of possible amino acid modifications, in the absence of guidance as to the specific nature of modifications resulting in a functional polypeptide, does not allow the skilled artisan to make and use the claimed polypeptides commensurate in scope with the instant claims without undue experimentation." The Examiner appears to base the enablement rejection on the proposition that modifications to amino acids in a protein sequence may alter the biological activity of the protein and that Applicants have presented no guidance as to how to determine whether a protein sequence containing a modified amino acid (such as, e.g., a pegylated amino acid) bears the claimed functional property. These assertions wholly lack merit.

As discussed above, the specification provides clear guidance to one skilled in the art as to how to determine whether a polypeptide which comprises an extracellular domain (ECD) comprising an amino acid sequence having at least 91% sequence identity to the ECD of SEQ ID NO:66) has the functional characteristic specifically defined by these claims (i.e., a human CD28/human CTLA-4 binding affinity ratio about equal to or greater than the human CD28/human CTLA-4 binding affinity ratio of human B7-1 when the polypeptide is expressed on a cell or bound to a cell membrane). The assays for determining this binding affinity assay are described in full detail. The fact that an amino acid in a protein sequence is modified makes no difference. The same biological assays would be used to test whether the protein had the requisite binding affinity ratio. Based upon the teachings of the specification, including the numerous working examples, the abundant guidance provided in the specification, specifically defined nature of the invention, the

state of the art, and the level of skill in the art at the time the application was filed, one of ordinary skill in the art to which this application pertains would surely have been reasonably able to determine whether a polypeptide (including one containing an amino acid that has been modified by, e.g., pegylation) possesses the characteristics of claims 289 and 290 – including the specified binding affinity ratio. No undue experimentation whatsoever would have been required.

Furthermore, even if some experimentation would have been necessary to make and use the claimed polypeptides, which Applicants do not believe, such experimentation would clearly not support an enablement rejection of claims 289 and 290. *In re Wands*, 858 F.2d at 731 (Fed. Cir., 1988); *Atlas Powder*, 750 F.2d at 1569 (Fed. Cir, 1984). However, as noted above, the enablement requirement can be met even if some experimentation is necessary, if such experimentation is not "unduly extensive." *Atlas Powder*, 750 F.2d at 1576. Clearly, no unduly extensive experimentation would be needed to make and use the polypeptides defined by claims 289 and 290.

For at least these reasons, Applicants submit the rejection is improper. Withdrawal of the rejection is respectfully requested.

## VII. REJECTIONS UNDER 35 USC § 102(B)

Claims 259-262, 264-267, 271, 277, 281, 283-286, 288, 297-298, and 368 were rejected under 35 UCS § 102(b) as allegedly being anticipated by Parsons *et al.*, *Immunogenetics* 49:231-234 (1999) ("Parsons"). Office Action, page 11. The Examiner finds that Parsons teaches the sequence of cattle CD80 protein, which is 90% identical in sequence to amino acids 35-242 of SEQ ID NO:66. *Id.* Based on this finding, the Examiner concludes that "the teachings of Parsons et al. anticipate the claimed limitations of 'at least about 91% (or 95%) sequence identity' to the extracellular domain of SEQ ID NO:66. The claimed functional limitations of binding affinity or inducing T-cell proliferation would be inherent properties of the referenced polypeptide." *Id.* at pages 11-12. The Examiner also asserts that claim 368 is included "because a polypeptide taught by Parsons et al. sharing extensive stretches of amino acid sequence identity with the polypeptide of SEQ ID NO:66 would necessarily, be specifically bound by a polyclonal antisera raised against a polypeptide of claim 259." *Id.* at page 12. This rejection is respectfully traversed.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of anticipation under § 102(b) with respect to the cited reference. In order for a prior art reference to anticipate an invention, the ***reference must teach each and every limitation of the***

***claimed invention either expressly or inherently.*** The Examiner has not explicitly shown (and Applicants believe cannot show) that Parsons teaches each and every element of any of the rejected claims expressly or inherently. Of the rejected claims, only claims 259, 284, and 297 are independent. A *prima facie* case of anticipation has not been properly established for any of these claims as discussed in detail below.

**A. Claim 259 and claims dependent thereon**

As previously drafted, independent claim 259 specifies:

> An isolated or recombinant polypeptide comprising an extracellular domain, said extracellular domain comprising an amino acid sequence having at least about 91% sequence identity to a subsequence of the polypeptide sequence set forth in SEQ ID NO:66, wherein the subsequence is the extracellular domain of SEQ ID NO:66, and wherein the isolated or recombinant polypeptide has a human CD28/human CTLA-4 binding affinity ratio about equal to or greater than the human CD28/human CTLA-4 binding affinity ratio of human B7-1 when expressed on a cell or bound to a cell membrane.

Applicants submit that the Action has not shown where Parsons taught or suggested each and every element of claim 259. For example, it has not been shown that Parsons taught or suggested a polypeptide comprising an extracellular domain (ECD) that comprises an amino acid sequence that is ***at least about 91% identity*** to the ECD of SEQ ID NO:66. On the contrary, the Examiner concedes that cattle CD80 protein shown in Parsons is only 90% identical in sequence to residues 35-242 of SEQ ID NO:66. Thus, by the Examiner's own admission, the protein sequence of cattle CD80 protein is **not** at least about 91% identical to the ECD of SEQ ID NO:66 and the teachings of Parsons do **not** anticipate claim 259.

Furthermore, the Action has not shown that Parsons teaches or suggests such a polypeptide that is at least about 91% identical to the ECD of SEQ ID NO:66 and *that has a human CD28/human CTLA-4 binding affinity ratio about equal to or greater than that of human B7-1.* The Examiner's contention that the functional limitations relating to binding affinity ratio (as in claim 259) or induction of T-cell proliferation (as in dependent claim 283) would be an inherent property of the referenced polypeptide is misplaced. The law is clear that a prior art reference may anticipate without disclosing a feature of the claimed invention if that characteristic is *necessarily present* in the single anticipating reference (*i.e.*, the natural result flowing from the explicit disclosure of the prior art reference). *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). For inherent anticipation, the reference must sufficiently describe and enable at least one

embodiment that necessarily feature or result in the subject matter embraced by the limitation. *Toro Co. v. Deere & Co.*, 355 F.3d 1313 (Fed. Cir. 2004), *rehearing denied,* 2004 U.S. App. LEXIS 4125 (Fed. Cir., Feb. 13, 2004). The Examiner has not shown any teaching or suggestion in Parsons that the ECD of cattle CD80 necessarily has or produces a human CD28/human CTLA-4 binding affinity ratio that is about equal to or greater than the human CD28/human CTLA-4 binding affinity ratio of human B7-1. At best, Parsons shows only that cattle CD80 comprises an ECD (if one assumes the ECD corresponds to the same region as in human B7-1) that is only 90% identical to the ECD of SEQ ID NO:66 and that is capable of binding mouse CTLA-4Ig. Nor has any teaching or suggestion been identified in Parsons that the ECD of cattle CD80 necessarily induces a T-cell proliferation response about equal to or greater than the T-cell proliferation response induced by human B7-1.

Amended claim 259 is also not anticipated by Parsons. As amended, claim 259 specifies more particularly that the isolated or recombinant polypeptide comprises an ECD comprising a sequence having *at least 91% sequence identity* to the ECD of SEQ ID NO:66 and has a human CD28/human CTLA-4 binding affinity ratio equal to or greater than the human CD28/human CTLA-4 binding affinity ratio of human B7-1 when the isolated or recombinant polypeptide is expressed on a cell or bound to a cell membrane. Parsons does not teach or suggest such a polypeptide sequence.

Moreover, a claim that specifies a polypeptide comprising an ECD that has ***at least about 95% sequence identity*** to the ECD of SEQ ID NO:66 is clearly not anticipated by Parsons (see, e.g., dependent claims 261 and 262). By the Examiner's own admission, Parsons discloses cattle CD80 protein comprising an ECD that shares only 90% sequence identity with the ECD of SEQ ID NO:66. The Examiner has not shown (and Applicants believe cannot show) that Parsons discloses or suggests a polypeptide comprising an ECD that has *at least about 95% sequence identity* to the ECD of SEQ ID NO:66, wherein the predicted ECD comprises residues 35-244 or residues 35-245 of SEQ ID NO:66. Indeed, Parsons does not disclose such a polypeptide. Nor has the Examiner shown (and Applicants believe cannot show) that Parsons teaches or suggests that such a polypeptide has a human CD28/human CTLA-4 binding affinity ratio equal to or greater than the human CD28/human CTLA-4 binding affinity ratio of human B7-1 when such polypeptide is expressed on a cell or bound to a cell membrane.

Nor can it be shown that Parsons discloses all of the limitations of amended claims 261 and 262, which recite more particularly the polypeptide comprises an ECD which comprises a sequence having *at least 95% sequence identity* to the ECD of SEQ ID NO:66.

Additionally, the Examiner has also not shown that Parsons teaches that cattle CD80 has a signal sequence that is identical to residues 1-34 of SEQ ID NO:66, as in claim 266. In fact, as shown by the Examiner's search results, the signal sequence of cattle CD80 differs from that of SEQ ID NO:66 by at least one amino acid residue (see position 9).

Nor has it been shown that Parsons teaches or suggests the polypeptide of dependent claim 277. The Examiner has not been shown (and Applicants believe cannot show) that Parsons discloses a polypeptide which comprises a sequence that is *at least about 90% identical to the amino acid sequence corresponding to the signal peptide, ECD, and transmembrane domain of SEQ ID NO:66* (which comprises at least amino acid residues 1-268 or 1-272 of SEQ ID NO:66), wherein the ECD has at least 91% sequence identity with the ECD of SEQ ID NO:66. On the contrary, taken together, the putative signal sequence, ECD and transmembrane domain of the cattle CD80 protein taught in Parsons constitute a polypeptide sequence that is ***even less than 90% identical*** to a polypeptide sequence comprising the same domains of SEQ ID NO:66.

Nor can it be shown that Parsons discloses the limitations of amended claim 277, which more particularly specifies the polypeptide comprises a sequence having *at least 90% sequence identity to the to the amino acid sequence corresponding to the signal peptide, ECD, and transmembrane domain of SEQ ID NO:66.*

Because independent claim 259 is not anticipated by Parsons, no claim dependent upon claim 259 (including claim 368) is anticipated by that reference.

For at least these reasons, Applicants respectfully submit that the requirements for a *prima facie* case of anticipation have not been met for independent claim 259 and claims 260-262, 264-267, 271, 277, 281, 283, 288, 298, and 368 dependent thereon. The rejection is improper and its withdrawal is respectfully requested.

**B. <u>Claim 284 and claims dependent thereon</u>**

Likewise, for similar reasons, Applicants submit that the requirements for a *prima facie* case of anticipation have not been met for independent claim 284 and claims dependent thereon. As previously drafted, claim 284 recites:

> An isolated or recombinant polypeptide comprising an extracellular domain, said extracellular domain comprising an amino acid sequence having at least about 91% sequence identity to a subsequence of SEQ ID NO:66, said subsequence comprising at least amino acid residues 35-244 or 35-245 of SEQ ID NO:66, wherein said polypeptide induces a T-cell proliferation response about equal to or greater than the T-cell proliferation response induced by human B7-1 when expressed on a cell or bound to a cell membrane.

The Examiner has not shown that Parsons teaches or suggests an isolated or recombinant polypeptide that comprises an ECD domain comprising an amino acid sequence *having at least about 91% sequence identity (or having at least 91% sequence identity as recited in amended claim 284)* to a sequence comprising at least amino acid residues 35-244 or 35-245 of SEQ ID NO:66. In fact, as the Examiner concedes, the putative ECD of cattle CD80 disclosed in Parsons shares *only 90% sequence identity* with the ECD of SEQ ID NO:66.

Moreover, it has not been shown that Parsons discloses or suggests that such a polypeptide, when expressed on a cell or bound to a cell membrane, induces a T-cell proliferation response about equal to or greater than the T-cell proliferation response induced by human B7-1 (or equal to or greater than the T-cell proliferation response induced by human B7-1 as recited in amended claim 284). The argument that Parsons inherently discloses a sequence with such functional properties is without merit. Parsons does not disclose the polypeptide of claim 284 comprising an ECD having at least 91% identity to residues 35-24 of SEQ ID NO:66. Additionally, the Examiner has not provided any evidence that the ECD of the claimed polypeptide or even the ECD of cattle CD80 necessarily induces a T-cell proliferation response equal to or greater than that induced by human B7-1 when said ECD is expressed on a cell or bound to a cell membrane.

Nor do Applicants believe it can be shown, e.g., that Parsons teaches or suggests all of the limitations in amended claim 285, which states that the ECD of the polypeptide of claim 284 comprises an amino acid sequence *having at least 95% sequence identity* to the subsequence of SEQ ID NO:66 comprising at least amino acid residues 35-244. Similarly, it been not shown that Parsons teaches all of the limitations of claim 286, which is dependent on claim 284.

For at least these reasons, Applicants respectfully submit that a *prima facie* case of anticipation has not been made for claim 284 and claims 285 and 286 dependent thereon. The rejection is improper and its withdrawal is respectfully requested.

C. **Claim 297**

As previously drafted, claim 297 recites:

> An isolated or recombinant polypeptide comprising an amino acid sequence having at least about 91% sequence identity to the complete amino acid sequence set forth in SEQ ID NO:66, wherein said polypeptide when expressed on a cell or bound to a cell membrane has a human CD28/human CTLA-4 binding affinity ratio at least about equal to the human CD28/human CTLA-4 binding affinity ratio of human B7-1 or induces a T-cell proliferation or activation response.

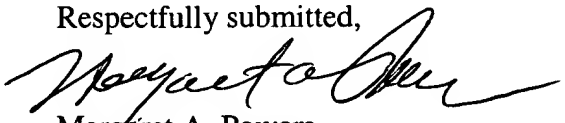
A *prima facie* case of anticipation has not been demonstrated for claim 297. It has not been shown that Parsons teaches or suggests an isolated or recombinant polypeptide comprising a sequence *having at least about 91% sequence identity (or having at least 91% sequence identity to the complete amino acid sequence as recited in amended claim 297)* to the complete amino acid sequence of SEQ ID NO:66. In addition, it has not been shown that Parsons discloses or suggests that such a polypeptide wherein said polypeptide when expressed on a cell or bound to a cell membrane has a human CD28/human CTLA-4 binding affinity ratio at least about equal to (or equal to as recited in amended claim 297) the human CD28/human CTLA-4 binding affinity ratio of human B7-1 or induces a T-cell proliferation or activation response. The argument that the Parsons reference inherently discloses a sequence with such functional properties is misplaced. The Examiner has not provided any evidence that the ECD of cattle CD80 disclosed in Parsons, when expressed on a cell or bound to a cell membrane, necessarily induces a T-cell proliferation response equal to or greater than that induced by human B7-1.

For at least these reasons, Applicants respectfully submit that a *prima facie* case of anticipation has not been made for claim 297 and the rejection is thus improper. Withdrawal of the rejection is respectfully requested.

## CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5809.

Respectfully submitted,



Margaret A. Powers
Attorney for Applicants
Reg. No. 39,804

March 21, 2005
Maxygen, Inc.
Intellectual Property Department
515 Galveston Drive
Redwood City, CA 94063
Telephone: 650-298-5809
Facsimile: 650-298-5446
Customer No. 30560

## APPENDIX

Attached hereto are the following:

1. A replacement sheet 23/37 for Figures 8A and 8B and an annotated sheet showing changes to the figures

2. A replacement sheet 25/39 for Figures 9G and 9H and an annotated sheet showing changes to the figures

**AMENDMENTS TO THE DRAWINGS:**

Following submission of the formal drawings to the Official Draftsperson of the USPTO on November 26, 2001, Applicants discovered several errors were inadvertently introduced into the formal drawings for Figures 8A, 8B, 9G, and 9H that were prepared based on the correctly drawn informal drawings originally filed with the application. As discussed below, these errors have been corrected in the replacement drawings submitted herewith.

**I. CORRECTIONS TO FIGURES 8A AND 8B**

In the informal drawings for Figures 8A and 8B originally filed with the application on June 22, 2001, the correct and complete clone name for each of the two protein sequences shown in these figures was provided. Specifically, the informal drawing for Figure 8A shows the protein sequence of clone (correctly) named "CTLA-4BP-5x4-12" and the informal drawing for Figure 8B shows the protein sequence of the clone (correctly) named "CD28BP-15". In the formal drawings subsequently submitted for Figures 8A and 8B (sheet 23/39), the correct complete name for each clone was not provided; only part of each clone name was included. These errors were inadvertent and were introduced during the preparation of the formal drawings. Attached hereto in the Appendix is a replacement sheet for Figures 8A and 8B (replacement sheet 23/39), which shows the complete and correct name for each clone – that is, CTLA-4BP-5x4-12 and CD28BP-15. The Appendix also includes an annotated sheet showing these changes to the clone names in Figures 8A and 8B.

In addition, the informal drawing for Figure 8B originally filed with the application correctly shows a dashed line below a predicted transmembrane domain, as explained in the specification at page 199, lines 8-11. This predicted transmembrane domain began with leucine (L) at amino acid residue position 246 of the CD28BP-15 protein sequence and comprised the following residues: LPFWVIIPVSGALVLTAVVLYCLACRH. See originally filed Figure 8B. Similarly, the predicted transmembrane domain for Fig. 8A (CTLA-4BP 5x4-12C) should begin at leucine (L), as shown in originally filed Fig. 8A (one amino acid residue prior to the proline shown in the subsequently submitted formal drawing).

In the formal drawing subsequently submitted for Figure 8B, the dashed line under the sequence indicating this predicted transmembrane domain was incorrectly drawn under only a portion of this predicted transmembrane domain (i.e., GALVLTAVVLYCLACRH). This error was inadvertent and was introduced preparation of the formal drawing for Figure 8B.

The replacement sheet for Figure 8B (replacement sheet 23/39), attached hereto in the Appendix, shows the dashed line under residues LPFWVIIPVSGALVLTAVVLYCLACRH of the CD28BP-15 sequence, a predicted transmembrane domain for CD28BP-15 shown in the informal drawing for Figure 8B filed as originally filed. The annotated sheet for these figures attached hereto shows this change (i.e., shows the additional dashed line included below preceding residues LPFWVIIPVS of the CD28BP-15 sequence).

The changes are consistent with the informal drawings for Figures 8A and 8B filed originally filed with the application, and no new matter is introduced by these amendments. Entry of these amendments is respectfully requested.

## II. CORRECTIONS TO FIGURES 9G AND 9H

In the informal drawings for Figures 9G and 9H originally filed with the application, the histograms for CTLA-4BP 5x4-12c (Fig. 9G) and human B7-1 (Fig. 9H) were properly shown in gray, while the negative control transfectants were properly shown as open histograms (without color), as expressly described in the specification, at page 201, line 30 to page 202, line 2. In the formal drawings subsequently filed, the histograms for CTLA-4BP 5x4-12c (Fig. 9G) and human B7-1 (Fig. 9H) were incorrectly shown as open (without gray color). These errors were inadvertent and were introduced during preparation of the formal drawings.

The replacement sheet for Figures 9G and 9H (replacement sheet 25/39), attached hereto in the Appendix, correctly shows the histograms for CTLA-4BP 5x4-12c (Fig. 9G) and hB7-1 (Fig. 9H) depicted in gray, with the negative control transfectants properly shown as open histograms (without color). The annotated sheet for these figures attached hereto shows these changes, which are consistent with the specification and Figures 9G and 9H as originally filed. These changes are consistent with the informal drawings for Figures 9G and 9H that were originally filed with the application, and no new matter is introduced by these amendments. Entry of these amendments is respectfully requested.

Fig. 8A

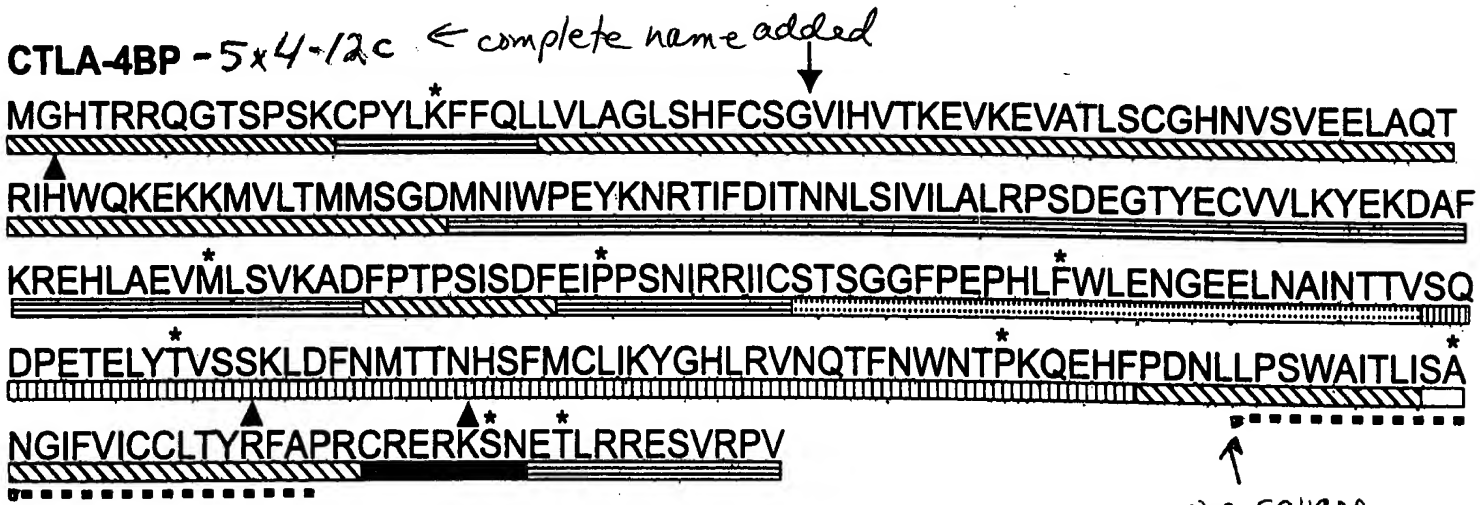
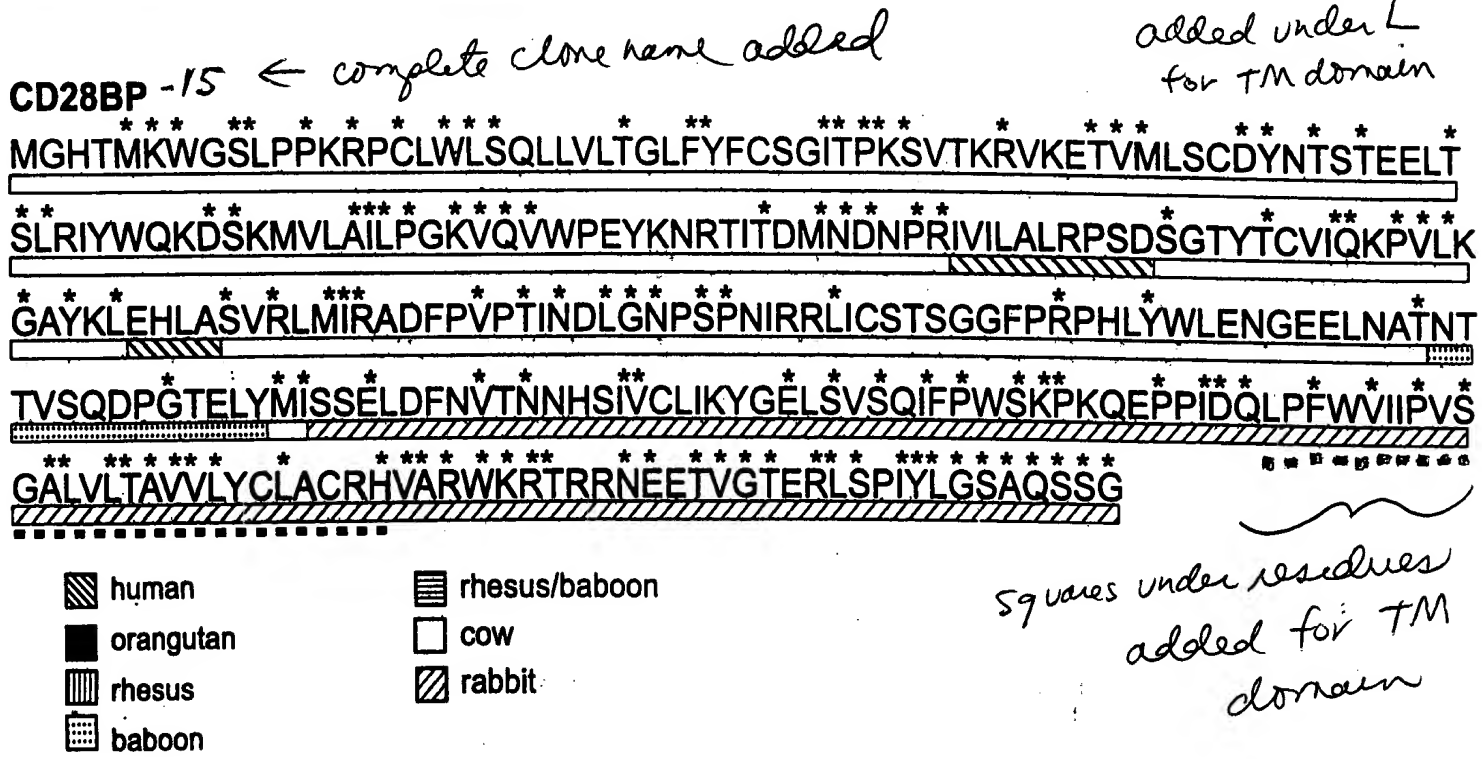



Fig. 8B



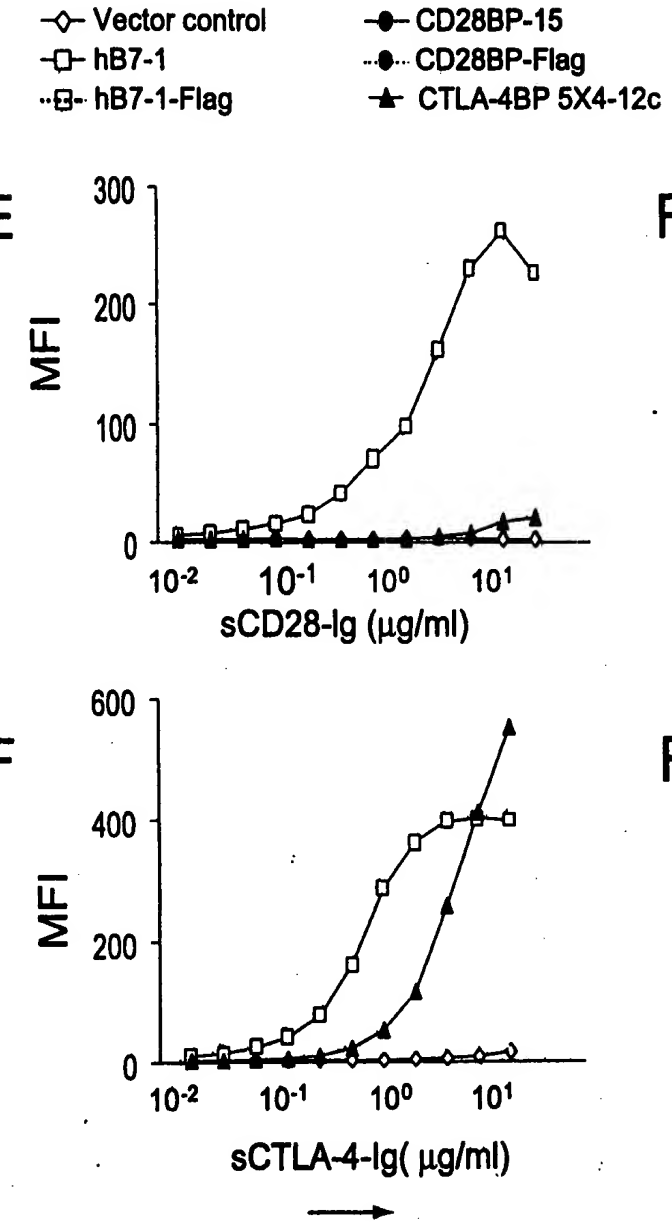



Fig. 9E




Fig. 9F

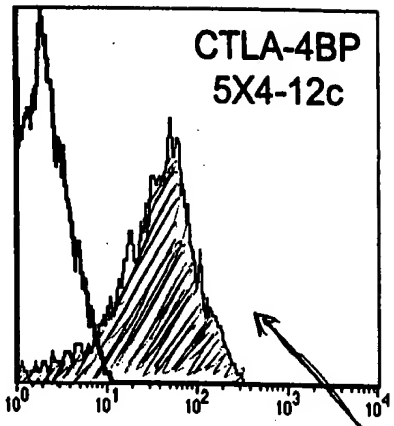



Fig. 9G

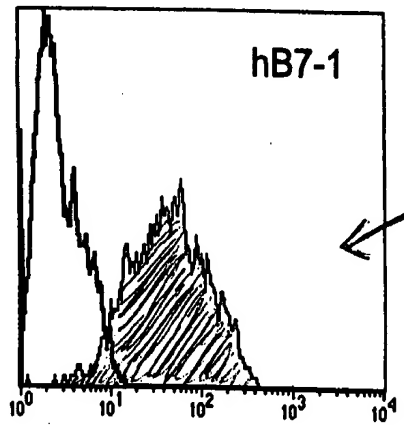



Fig. 9H

should be gray (solid color)